Botulinum Toxin Use in Neurourology

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The use of botulinum toxin A (BTX-A) has revolutionized the treatment of neurogenic lower urinary tract dysfunction (NLUTD) over the past three decades. Initially, it was used as a sphincteric injection for detrusor sphincter dyssynergia but now is used mostly as intradetrusor injection to treat neurogenic detrusor overactivity (NDO). Its use is supported by high-level-of-evidence studies and it has become the gold-standard treatment for patients with NDO refractory to anticholinergics. Several novelties have emerged in the use of BTX-A in neurourology over the past few years. Although onabotulinumtoxinA (BOTOX®, Allergan, Inc., Irvine, CA) remains the only BTX-A for which use is supported by large, multicenter, randomized, controlled trials (RCT), and is therefore the only one to be licensed in the United States and Europe, a second BTX-A, abobotulinumtoxinA (Dysport®, Ipsen Biopharmaceuticals, Basking Ridge, NJ), is also supported by high-level-of-evidence studies. Other innovations in the use of BTX-A in neurourology during the past few years include the BTX switch (from abobotulinumtoxinA to onabotulinumtoxinA or the opposite) as a rescue option for primary or secondary failures of intradetrusor BTX-A injection and refinements in intradetrusor injection techniques (number of injection sites, injection into the trigone). There is also a growing interest in long-term failure of BTX-A for NDO and their management, and a possible new indication for urethral sphincter injections.

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KEY WORDS

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Botulinum toxin (BTX) is a neurotoxin produced by *Clostridium botulinum*, a gram-positive, rod-shaped anaerobic bacterium.[1] There are seven immunologically distinct neurotoxins designated as types A to G. Initially isolated by researchers from Fort Detrick, Maryland, to be used as a possible biological weapon during World War II, the A serotype of BTX (BTX-A) has been shown as the one of the seven subtypes with a more prolonged therapeutic effect and is currently the most widely used as a medical therapy. This is based on the pioneering work of the San Francisco ophthalmologist Alan B. Scott in the 1970s.[1-2] BTX-A has been used in neurogenic lower urinary tract dysfunction (NLUTD) for over three decades and began with the work of Denis Dykstra, who reported the first sphincter injections for detrusor sphincter dyssynergia in 1988.[3] This was followed by studies lead by Brigitte Schurch, who reported the first intradetrusor injection for NDO in patients with spinal cord injury (SCI) and multiple sclerosis (MS) in 2000.[4] Since then, BTX-A has revolutionized the management of NLUTD and has been widely assessed through randomized, controlled trials (RCTs) for the two aforementioned indications. It has also been evaluated for neurologic conditions that were not included in the initial studies (eg, Parkinson's disease, spina bifida) and several technical refinements in its use have been described and assessed.[5] This article provides an overview of the use of BTX-A for NLUTD, including its high-quality evidence base and recent relevant insights.

Methods

A PubMed-based literature search was conducted in December 2017, screening for RCTs and prospective and retrospective series on the use of BTX in neurourology. The search strategy included the terms *toxin*, *neurogenic*, *neuropathic*, *neurologic*, *BOTOX*, *disport*, *detrusor*, *bladder*, *sphincter*, *intradetrusor*, *spinal cord injury*, *multiple sclerosis*, *spina bifida*, *Parkinson's*, *cerebrovascular accident*, and *stroke* that were used alone or in combination. Only articles published in English and deemed relevant were included.

Results

Basic Principles of BTX Mechanism of Action

BTX-A action when injected in the lower urinary tract (either bladder or sphincter) has for long been thought to rely mostly on its known effect of blocking the presynaptic vesicular release of acetylcholine (ACh) at the neuromuscular junction. However, evidence from the past decade have demonstrated a dual mode of action for intradetrusor injections on both the afferent and efferent pathways.[6]

At the molecular level, BTX-A is known to block presynaptic neurotransmitter release by binding to gangliosides, interact with synaptic vesical protein 2 (SV2), and for subsequent cleavage of the SNAP25 protein (synaptosomal-associated protein with a molecular weight of 25 kDa), which is necessary for fusion of the synaptic vesicles at the cellular membrane, thereby preventing the SNARE–mediated exocytosis of several neurotransmitters [ACh, substance P, adenosine triphosphate (ATP)] into the synaptic cleft.[6,7] In addition to its effect on the efferent cholinergic and purinergic pathways (ACh, ATP), BTX-A produces an afferent desensitization through the purinergic pathway (ATP and P2X3 receptors) and decrease of TRPV1 receptors as well as its possible action on neurotrophins (nerve growth factor and brain-derived neurotrophic factor). It has also been shown to inhibit exocytosis of sensory peptides such as substance P and calcitonin-gene related peptide (CGRP) from sensory neurons.[6-7]

In contrast with the dual afferent and efferent mechanism of action seen in intradetrusor injections, sphincter injections are assumed to work primarily through an efferent mechanism by blocking ACh release from presynaptic vesicles at the neuromuscular junction.[7]

Intradetrusor Injections for Neurogenic Detrusor Overactivity

Brigitte Schurch: Pioneering Works. In the 2000s, Brigitte Schurch and Manfred Stohrer reported for the first time the use of intradetrusor injections of onabotulinumtoxinA to treat NDO.[4,8] In their series that included 21 SCI patients with NDO refractory to anticholinergics from two institutions (Zurich, Switzerland and Murnau, Germany), they observed resolution of incontinence in 90.5% of patients and significant improvement of all urodynamic parameters 6 weeks after the injection of either 200 U or 300 U of onabotulinumtoxinA (BOTOX®, Allergan, Inc., Irvine, CA) and this effect was maintained at 36 weeks during the last follow-up visit.[4,8] Subsequently, Schurch led a prospective, multicenter, European study that included 200 neurogenic patients, mostly with SCI, who received intradetrusor injections of 300 U of onabotulinumtoxinA.[9] The results of this largest series reported in 2004 confirmed the preliminary findings with 73.3% of patients experiencing complete resolution of their urinary incontinence and improvement in all relevant urodynamic parameters at 12 and 36 weeks.[9] Finally, in 2005, Brigitte Schurch published the first phase 3 RCT demonstrating, with a high level of evidence, the ability of

intradetrusor onabotulinumtoxinA to treat NDO effectively in patients with SCI and MS.[10] It should be noted that all initial work was done in patients with NLUTD who were self-catheterization dependent.

Placebo-controlled, Randomized Trials. After the first RCT published in 2005 by Schurch and colleagues,[10] five other placebo-controlled randomized trials (ie, 6 in total) have aimed to assess the safety and efficacy of intradetrusor BTX-A injections in NDO patients.[11-15] The data of these six RCTs are summarized in Table 1. Two of these six RCTs were the phase 3 DIGNITY (Double-blind InvestiGation of purified Neurotoxin complex In neurogenic deTrusor overactivitY) trials that lead to the approval of intradetrusor onabotulinumtoxinA in NDO by regulatory authorities worldwide in 2011.[13-14] Several post-hoc cumulative analyses of the two DIGNITY RCTs have been published,[16-17] but their findings are not presented here because the data used were those already reported by Cruz and Ginsberg, respectively.[13-14] Five of the six RCTs published to date involved the use of onabotulinumtoxinA (BOTOX) whereas only one small sample size (n = 31) trial was performed with abobotulinumtoxinA (Dysport®, Ipsen Biopharmaceuticals, Inc., Basking Ridge, NJ). Larger phase 3 RCTs with abobotulinumtoxinA are ongoing. All these studies showed statistically significant improvement in symptoms (urinary incontinence episodes), quality of life, and urodynamic parameters (maximum detrusor pressure, maximum cystometric capacity, volume at first DO) 6 weeks after the injection with efficacy lasting more than 6 months and few adverse events confirming the good safety profile of intradetrusor onabotulinumtoxinA.[10-15]

TABLE 1

Evidence From Randomized Controlled Trials of Botulinum Toxin Versus Placebo in Patients With Neurogenic Detrusor Overactivity

Study	Patients (n)	Neurological Conditions of Included Patients	Treatment Arms & BTX-A Doses	Mean Change in Number of UI Episodes/Week at 6 Weeks	Mean Change in MCC (mL) at 6 Weeks	Mean Change in MDP (cm H_2O) at 6 Weeks
Schurch (2005)[10]	59	SCI (89.8%), MS (10.2%)	Placebo: 21 OnaBTX-A 200 U: 19 OnaBTX-A 300 U: 19	−0.2 −0.9 −1.5*	+45 +182.1* +169.1*	−10.1 −44.4* −62.2
Ehren (2007)[11]	31	SCI (80%), MS (19.4%), MMC (5.6%)	Placebo: 14 AboBTX-A 500 U: 17	Lower number of days with leakage in the treatment arm*	+10 +180*	−12 −52*
Herschorn (2011)[12]	57	SCI (66.7%), MS (33.3%)	Placebo: 28 OnaBTX-A 300 U: 29	+0.73 −1.75*	−29 +225*	+13 −27.5*
Cruz (2011)[13]	275	MS (56%), SCI (44%)	Placebo: 92 OnaBTX-A 200 U: 92 OnaBTX-A 300 U: 91	−1.9 −3.1* −2.8*	+6.5 +157* +157.2*	+6.4 −28.5* −26.9*
Ginsberg (2012)[14]	416	MS (54.6%) SCI (45.4%)	Placebo: 149 OnaBTX-A 200 U: 135 OnaBTX-A 300 U: 132	−1.2 −3* −3.2*	−2.4 −35.1* −33.3*	+16 +151* +168*
Apostolidis (2013)[15]	73	SCI (100%)	Placebo: 16 OnaBTX-A 50 U: 19 OnaBTX-A 100 U: 21 OnaBTX-A: 200 U: 17	−1.2 −1.1 −2* −2.3*	−2.1 −20.1 −29.4* −33*	+117.4 +136.8 +220.1 +183.7

* *P* value <0.05 for comparison of change from baseline vs placebo

AboBTX, abobotulinum toxin A; MCC, maximum cystometric capacity; MDP, maximum detrusor pressure; MMC, myelomeningocele; MS, multiple sclerosis; OnaBTX-A, onabotulinum toxin A; SCI, spinal cord injury; UI, urinary incontinence.

What Is the Optimal Dosing for Intradetrusor Injection in NDO?

Most of the placebo-controlled, randomized trials aimed to address the issue of the optimal dose to inject by including groups with various doses of onabotulinumtoxinA.[10-15] None of the three RCTs comparing onabotulinumtoxinA 200 U and 300 U reported clinically relevant differences in efficacy or duration of effect between the two doses which led to label the 200 U dose.[10,13,14] It should be noted that one of these studies included only catheter-dependent patients,[10] whereas the two others[13,14] included a proportion of MS patients who were not catheterizing. Although not supported by high-level-of-evidence studies,[13,14] some expert opinions and retrospective series data in the literature still suggest that the 300 U dosage could provide benefits over the 200 U dose in subset of patients poorly responsive to the 200 U dose,[18] or when considering "real-life" cohorts with patients excluded from the RCTs (eg, spina bifida, SCI above the T1 level).[19] However, Apostolidis and colleagues hypothesized in a randomized, placebo-controlled, dose-exploration study that lower doses of onabotulinumtoxinA (ie, 50 or 100 U) may achieve the same outcomes than the 200-U dose.[15] Evidence suggesting a significant linear dose response favoring onabotulinumtoxinA 200 U and significant improvements versus placebo were noted in several efficacy parameters; their findings suggested that a 200-U dose was required to achieve adequate efficacy in SCI patients.[15] Conversely, a recent and still unpublished RCT demonstrated significant and clinically meaningful improvement of urinary incontinence and urodynamic parameters using onabotulinumtoxinA 100 U versus placebo in non–self-catheterizing MS patients with a clean intermittent catheterization (CIC) rate of only 15.2% in the treatment arm, suggesting that a 100-U dose might be a relevant option in these MS patients to preserve voiding.[20] These two later studies helped to clarify the dosing uncertainty for MS and SCI patients, inherent to the indistinct inclusion of NDO patients voiding spontaneously versus with CIC in the DIGNITY trials.[13,14] Finally, evidence is too scarce to recommend any specific toxin doses to treat patients with NDO related to suprapontine diseases (eg, Parkinson disease, cerebrovascular accident).

Injection Techniques. Various injection techniques have been described, with main differences concerning the types of cystoscope used (rigid vs flexible), anesthesia (local vs general), the facilities (operating room vs office), and injection sites even though most techniques involved injections distributed over the bladder wall. Injecting into the trigone has raised concerns regarding possible vesico-ureteral reflux, with most of initial studies reporting the use of a trigone-sparing approach.[21-23] Although strictly theoretical, the trigone-sparing approach became the standard as results were good and morbidity was low. Recent findings have challenged this dogma and suggest that protocols include the trigone as this could have additional sensory benefits as the trigone has a high density of nociceptive bladder afferents.[24]

The recommended dilution protocol for NDO is 200 U or 300 U onabotulinumtoxinA/30 mL of sterile 0.9% saline solution injected in 30 sites. However, the most common dilution protocol in daily practice is 10 U onabotulinumtoxinA/mL of sterile 0.9% saline solution and most teams have for long injected 1 mL/10 U per site resulting in a 20 to 30 injection site protocol for 200 U and 300 U of onabotulinumtoxinA, respectively.[21-23] Recent randomized trials have suggested that protocols with lower number of injection sites could provide similar efficacy.[25] In a recent prospective study, Avallone and colleagues reported promising outcomes administering BTX-A through only one to three injection sites, but further data are needed to confirm their findings as their cohort included a mix of OAB and NDO patients and had no control group.[26] Finally, onabotulinumtoxinA has usually been administered into the detrusor to treat NDO using needles typically 22 to 27 gauge and equal to 4 mm in length but, as evidenced in OAB and interstitial cystitis, one RCT found no significant difference between suburothelial and intradetrusor injections in NDO patients.[27]

Efficacy of Intradetrusor BOTOX in Other Neurogenic Populations.

As emphasized above, the neurological conditions of patients included in NDO RCTs were mostly SCI and MS. The evidence to support the use of intradetrusor BTX-A in other NDO populations is scarcer, as detailed below.

- **Spina Bifida.** In a recent systematic review of the literature, Hascoet and colleagues found only 12 published series evaluating intradetrusor BTX-A in spina bifida patients, none of which were a randomized trial.[28] All these studies were performed in pediatric populations and evidenced a clinical improvement with resolution of incontinence in 32% to 100% of patients and an urodynamic improvement with a decrease in maximum detrusor pressure ranging from 32% to 54%, an increase of maximum cystometric capacity from 27%

to 162%, and an improvement in bladder compliance of 28% to 176%. Two studies suggested lower efficacy in patients with low compliance bladder compared with those with isolated detrusor overactivity. There were no significant complications related to BTX-A injections except urinary tract infections in 4% to 29% of patients. The authors concluded that intradetrusor injections of BTX-A could be effective to treat NDO in children with spina bifida, but this assumption is not supported by high-level-of-evidence studies and there is currently no data available in adult patients.[28]

- **Parkinson's Disease.** Only five small single-center series including 4 to 20 patients have reported efficacy and safety of intradetrusor BTX-A in patients with Parkinson's disease (PD) using onabotulinumtoxinA (100 U in two studies and 200 U in two studies) and abobotulinumtoxinA (500 U in one study). Likely due to the differences in toxins and doses used, the outcomes varied with urinary retention requiring CIC in 0% to 25% of patients and full resolution of incontinence in 37.5% of patients.[29] One of the main concerns about BTX use in PD patients is the inability of patients to self-catheterize due to tremor. Due to the low rate of CIC reported, this issue has been poorly assessed in the series.[29]
- **Cerebrovascular Accident.** No series have specifically addressed the outcomes of intradetrusor BTX-A in patients with NDO resulting from a cerebrovascular accident (CVA).[29] Only two series, from the same group, included patients with CVA among patients with other conditions. These studies reported poorer functional outcomes than in other neurogenic populations, with only 8% of patients with complete continence after onabotulinumtoxinA 100 U in the most updated series including 23 CVA patients, and 17.4% of urinary retention requiring CIC.[30] However, the toxin was administered in the suburothelium and not into the detrusor muscle.[30]
- **Other Neurological Conditions.** No series assessing the outcomes of intradetrusor BTX-A specifically in neurological conditions other than the above have been reported.[29]

Long-term Results. In a 3-year, open-label extension of the DIGNITY trials, Rovner and colleagues recently reported sustained efficacy of repeated intradetrusor injection in NDO patients up to 4 years with 88% and 90% of patients successfully treated with 1.4 to 1.5 treatments each year on average.[31] However, in their recent systematic review, Ni and colleagues observed that patients who had received ≤4 injections were found to have stable QOL improvements after the first and last injections, whereas patients who had received ≥5 injections were found to have a significant decrease in QOL after the last injection, suggesting that decreased efficacy of intradetrusor BTX-A injections could start after five injections.[32] In their recent series, Joussain and coworkers reported a 39.8% discontinuation rate and a 28.9% failure rate after a follow-up of 7 years,[33] confirming, in the largest cohort to date and with a remarkable methodology, recent findings from smaller series, with long-term discontinuation rates of up to 45.2%.[32] Likewise, in the series with the longest follow-up so far (>15 years) including the very first patients treated by Schurch and colleagues, Leitner and associates reported a 40% discontinuation rate.[34] Although discontinuation may be explained by progression of the neurological condition/impairment in patients with MS, two mechanisms have been hypothesized to explain long-term failures: formation of neutralizing antibodies, and histological changes of the bladder wall with repeated injections.[35] Antitoxin antibodies are a well-accepted cause of secondary resistance to BTX-A in several indications, with incidence reported to be as high as 20% for cervical dystonia and 5.9% for spasticity.[36] However, although botulinum neurotoxin (BoNT) use in urologic conditions has increased, little data exist on the risk of antibody formation in this patient population.[36] Assumptions have been made that progressively appearing fibrosis over consecutive injections may prevent normal spread of toxin into the bladder wall and explain secondary failures. However, data regarding histological changes induced by BTX-A intradetrusor injections would suggest that patients with BTX-A could conversely display less fibrosis than non-treated patients.[37]

Several experts advocate the reinjection of the same toxin at a higher dosage as a possible way to manage failure of BTX-A intradetrusor injections after initial success.[18] However, this option was widely used by Joussain and colleagues in their study (93 of 292 patients) and did not prevent a high failure or discontinuation rate. Despite a recent "real-life" retrospective series suggested that onabotulinumtoxinA 300 U might provide better outcomes than the 200-U dose,[19] this finding was not supported by data from the RCT that reported similar efficacy between the two doses. BTX switch has recently been proposed as another option to manage these failures.

BTX Switch. In 2004, two teams concomitantly proposed for the first time the use of another BTX as a rescue option in patients for whom intradetrusor BTX-A injections failed.[38,39] Postulating that the different antigenic specificity of BTX type B versus type A may skirt neutralizing antibodies in patients with secondary resistance to BTX-A, two series anecdotally reported a total of three cases of SCI patients who developed resistance to BTX-A bladder injections and were effectively treated with botulinum type B injections.[38,39] However, subsequent reports regarding the higher rate of systemic adverse effects, the shorter duration of action, and the high antigenicity of intradetrusor BTX-B have discouraged its use in NDO.[40]

In recent years, three studies from a French group have suggested that switching from one BTX-A brand to another (either from onabotulinumtoxinA to abobotulinumtoxinA or vice versa) could be effective in approximately 50% of failures.[41-43] In a preliminary study, Peyronnet and colleagues reported that a second injection of abobotulinumtoxinA 750 U after failure of a 300 U onabotulinumtoxinA injection was successful both clinically (resolution of incontinence and urgency) and urodynamically (resolution of detrusor overactivity) in 57.7% of 26 NDO patients.[41] In a second study, the same group showed a higher success rate when switching toxin type (one way or another) versus repeating a second injection of the same toxin in patients who failed a first injection.[42] Interestingly, patients treated with a switch from abobotulinumtoxinA to onabotulinumtoxinA and those treated with a switch from onabotulinumtoxinA to abobotulinumtoxinA had similar success rates (52.9% vs 50%, $P = .88$).[42] Finally, a third multicenter study evidenced consistent outcomes when assessing 57 NDO patients who were switched from onabotulinumtoxinA to abobotulinumtoxinA after primary or secondary failures with clinical and urodynamic success rates of 52.6% and 43.9%, respectively.[43] Table 2 summarizes data published to date regarding BTX switch in NDO patients. Despite these promising preliminary findings, BTX-A switch remains supported by only small retrospective series, and long-term data are lacking. The mechanism of action is still elusive as current evidence cannot entirely rule out the assumptions of either a dose equivalence issue or a cumulative effect.

AbobotulinumtoxinA. OnabotulinumtoxinA (BOTOX) is the only BTX for which use is supported by large, multicenter RCTs.[10,12-15] and therefore is the only one approved in the United States and Europe for the management of NDO.[1] However, the use of abobotulinumtoxinA (Dysport) for NDO is also supported by high-level-of-evidence studies,[11,25,44,45] and was used in several centers for intradetrusor injections. The data from prospective studies assessing abobotulinumtoxinA in NDO patients are shown in Table 3.

TABLE 2

Studies Reporting the Outcomes of Botulinum Toxin Switch

Study	Patients (n)	Primary vs Secondary Failure	Type of Switch	Clinical "Success" Rate	Urodynamic "Success" Rate
Pistolesi (2004)[38]	1	Secondary	BTX-A to BTX-B	100%	100%
Reitz (2004)[39]	2	Secondary	BTX-A to BTX-B	100%	100%
Peyronnet (2016)[41]	26	Primary	Abo-BTX A to Ona-BTX A	65.4%	57.7%
Peyronnet (2015)[18]	29	Primary	Abo-BTX A to Ona-BTX A and the opposite	51.7%	58.6%
Bottet (2018)[43]	57	Primary (38.6%) and secondary (61.4%)	Ona-BTX A > Abo-BTX A	52.6%	43.9%

Dysport®, Ipsen Biopharmaceuticals, Basking Ridge, NJ.
Abo-BTX A, abobotulinum toxin A; BTX-A, botulinum toxin type A; BTX-B, botulinum toxin type B; MMC, myelomeningocele; MS, multiple sclerosis; Ona-BTX A, onabotulinum toxin A; SCI, spinal cord injury.

TABLE 3

Evidence From Prospective Studies Regarding Outcomes of Intradetrusor Abobotulinum Toxin A in Patients With Neurogenic Detrusor Overactivity

Study	Patients (n)	Study Design	Treatment Arms & BTX-A Doses	Mean Change in Number of UI Episodes/Week at 4-6 Weeks	Mean Change in MCC (mL) at 4-6 Weeks	Mean Change in MDP (cm H_2O) at 4-6 Weeks
Ruffion (2006)[44]	45	Dose ranging prospective study assessing the effect of successive 500 U and 1000 U doses	AboBTX-A 500 U: 45 AboBTX-A 1000 U: 28	N/A	+192† +213*	–12 –29*
Ehren (2007)[11]	31	Randomized phase 2 placebo-controlled trial	Placebo: 14 AboBTX-A 500 U: 17	Lower number of days with leakage in the treatment arm*	+10 +180*	–12 –52*
Grise (2010)[45]	77	Dose-ranging prospective randomized trial	AboBTX-A 500 U: 39 AboBTX-A 750 U: 38	Complete continence: 56.4% vs 73.7%	+192.1† +243†	N/A N/A
Denys (2017)[25]	42	Randomized phase 2 placebo-controlled trial assessing 15 vs 30 injection sites	Placebo 15 inj: 6 AboBTX-A 750 U 15 inj: 14 Placebo 30 inj: 6 AboBTX-A 750 U 30 inj: 16	–1.2 –3.6 –1.7 –3.0	+45.6 +162.6 –27.0 +196.7*	–4.1 –39.2* +21.6 –29.4*

*P value <0.05 for comparison of change from baseline vs placebo.
†P value <0.05 for paired comparison vs baseline.
Abo-BTX A, abobotulinum toxin A; N/A, not available.

In 2006 and 2010, Ruffion and Grise published two prospective dose-ranging studies comparing injections of abobotulinumtoxinA at doses of 500 U versus 1000 U[44] and 500 U versus 750 U,[45] respectively. Their findings suggest that the 750-U dose had the best efficacy and safety profile as 1000 U–exposed patients to major complications (one general muscle weakness with asthenia) and 500 U tended to provide poorer outcomes.[44,45] Two small phase 2 trials assessing abobotulinumtoxinA in patients with NDO both showed statistically significant improvements in the number of urinary incontinence episodes, maximum cystometric capacity, maximum detrusor pressure, and volume at first contraction in the abobotulinumtoxinA groups compared with placebo ($P < .05$).[11,25] In terms of relative efficacy of abobotulinumtoxinA versus onabotulinumtoxinA in NDO patients, very few data are available.[19] In the largest comparative series to date, Peyronnet and colleagues found better outcomes after intradetrusor injections of abobotulinumtoxinA 750 U compared with injections of onabotulinumtoxinA 200 U for NDO. In contrast, success rates of abobotulinumtoxinA 750 U and onabotulinumtoxinA 300 U were similar, but the interval between injections tended to be longer with onabotulinumtoxinA 300 U, suggesting dose equivalence issues rather than one toxin's superiority to another.[19] AbobotulinumtoxinA is currently being investigated in two ongoing phase 3 RCTs (The CONTENT trials, NCT02660359 and NCT02660138), the results of which will help to better define the role of abobotulinumtoxinA in treating NDO.

Sphincter Injection

Detrusor Sphincter Dyssynergia. After the initial description in the

TABLE 4

Randomized Trials Evaluating Botulinum Toxin Sphincter Injections for Detrusor Sphincter Dyssinergia

Study	Patients (n)	Neurological Conditions of Included Patients	Treatment Arms & BTX-A Doses	Mean Change of PVR (mL) at 4-6 Weeks	Mean Change of MDP (cm H_2O) at 4-6 Weeks
Dykstra et al (1990)[47]	5	SCI	OnaBTX-A 140 U/240 U[a]: 3 Placebo: 2	−125 N/A	−30 N/A
De Seze et al (2002)[48]	13	SCI	OnaBTX-A 100 U: 5 Lidocaine: 8	−159.6 −50.2*	N/A N/A
Gallien et al (2005)[49]	86	MS	OnaBTX-A 100 U: 45 Placebo: 41	−14 −31	+4 −15*

[a] Weekly injection during 3 consecutive weeks (140 U; 240 U; 240 U).
*P value <0.05 for comparison of change from baseline vs placebo.
BTX-A, botulinum toxin A; MDP, maximum detrusor pressure; MS, multiple sclerosis; Ona-BTX A, onabotulinum toxin A; N/A, not available; PVR, post-void residual volume; SCI, spinal cord injury.

late 1980s by Dykstra and colleagues,[3] urethral sphincter injections of onabotulinumtoxinA have been used and assessed in several studies during the past two decades.[5,7] The aim of BTX-A injections into the external sphincter is to prevent increased sphincter activity during voiding and/or DO and thus improve voiding function while preventing high bladder pressure and upper urinary tract damage. This effect is obtained by acting on the efferent pathway with blockage of ACh release at the neuromuscular junction, achieving chemical denervation of the external sphincter.[5,7] The dose used ranged from 50 U to 200 U but in the vast majority of studies, 100 U of onabotulinumtoxinA was injected either under cystoscopic guidance or through a transperineal approach with or without electromyography guidance and under either local or general anesthesia.[46]

An alternative technique using transrectal ultrasound–guided, transperineal injection has also been described. Although a large randomized phase 3 trial is lacking, three small placebo-controlled, randomized trials have been reported, and their data are summarized in Table 4.[47-49] Although the two preliminary RCTs conducted by Dykstra and colleagues (5 SCI patients)[47] and De Seze and colleageus (13 SCI patients)[48] suggested significant decrease in post-void residual volume with sphincter injections of BTX-A versus placebo, the largest RCT to date randomizing 86 MS patients did not meet its primary endpoint of reduction in post-void residual volume.[49] This is in line with the overestimation of the effects of BTX-A in all indications observed in smaller/lower level of evidence studies versus well-designed larger RCTs.[50] As a result of the scarce aforementioned evidence, a recent Cochrane systematic review concluded that small studies with a high risk of bias have identified evidence of limited quality that intraurethral BTX-A injections improve some urodynamic measures after 30 days in the treatment of functional bladder outlet obstruction in adults with NULTD. They suggested that a surgical sphincterotomy might be a more effective treatment option for lowering bladder pressure in the long term.[51] Although BTX-A urethral sphincter injections are still used as a chemical sphincterotomy in some centers for patients unable to self-catheterize, current guidelines recommend favoring other options.[52]

Difficulties With Clean Intermittent Catheterization. In a recent, still unpublished, prospective study, a French group assessed the outcomes of BTX-A sphincter injections in 12 male neurogenic patients with blockage in the urethra, presumably due to increased tone of striated urethral sphincter, having difficulties performing CIC.[53] Evaluating patients' difficulties performing CIC using the validated Intermittent Catheterization Difficulty Questionnaire (ICDQ)[54] and the Patient Global Impression of Improvement (PGII), Honore and colleagues reported statistically significant facilitation of CIC 1 month after the transperineal urethral sphincter injection of onabotulinumtoxinA 100 U.[53]

Practical Considerations for Injections at Multiple Sites

A large cumulative dose of BTX-A (BoNT-A) has been suggested to be associated with a high incidence

of neutralizing antibodies and adverse events.[55] This is particularly relevant for patients who receive BTX-A for more than one indication (eg, spasticity and NDO). Although this assumption has not been supported in the available clinical data,[56] it is still recommended that patients should not have received therapeutic onabotulinumtoxinA (for any indication) in the previous 3 months and that the cumulative maximum dose of 360 U over a 3-month period (for all indications) should not be exceeded.[57] To decrease the theoretical risks of adverse events and neutralizing antibody formation due to multidisciplinary use and inherent cumulative dose use of BTX-A, some experts also suggest using the same BoNT formulation and injecting within 24 hours of each indication.[55]

Conclusions

The use of BTX-A has revolutionized neurourology during the past three decades, initially through sphincter injection for detrusor-sphincter dyssynergia, but also with intradetrusor injections that have become the gold-standard treatment for NDO patients who are refractory to anticholinergics. Several novel treatments have emerged in the use of BTX-A in neurourology over the past few years, including BTX switch as a rescue option, a second type of BTX-A, abobotulinumtoxinA, being assessed in ongoing phase 3 RCTs, refinements in intradetrusor injection techniques (number of injection sites, injection into the trigone), growing interest regarding long-term failures of BTX-A for NDO, and new indications for sphincter injections. ■

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MAIN POINTS

- The use of BTX-A has revolutionized neurourology during the past three decades, initially through sphincter injection for detrusor-sphincter dyssynergia, but also with intradetrusor injections that have become the gold-standard treatment for NDO patients who are refractory to anticholinergics.
- Several novel treatments have emerged in the use of BTX-A in neurourology over the past few years, including BTX switch as a rescue option; a second type of BTX-A, abobotulinumtoxinA, being assessed in ongoing phase 3 RCTs; refinements in intradetrusor injection techniques (number of injection sites, injection into the trigone); growing interest regarding long-term failures of BTX-A for NDO; and new indications for sphincter injections.

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